



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/706,555	11/12/2003	John W. Mickelson	PC27721A	6894
23913	7590	11/22/2005	EXAMINER	
PFIZER INC 150 EAST 42ND STREET 5TH FLOOR - STOP 49 NEW YORK, NY 10017-5612			TUCKER, ZACHARY C	
			ART UNIT	PAPER NUMBER
			1624	

DATE MAILED: 11/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/706,555

Applicant(s)

MICKELSON, JOHN W.

Examiner

Zachary C. Tucker

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 October 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) 6-13 and 17-21 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5 and 14-16 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 16Apr04.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION***Election/Restrictions***

Applicant's election of the invention of Group I in the reply filed on 12 October 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Further, the election of the compound 2-(2-chloro-4-methoxyphenyl)-3,6-diethyl-[(2S)-(methoxymethyl)pyrrolidin-1-yl]pyrazine is noted. This compound is disclosed on page 7 of the specification, at lines 22 and 23. All claims within the elected Group read on this species, so no claims have been withdrawn as not readable on the elected species. Claims 1, 2 and 14-16, however, have not been fully searched, because art was found and the search stopped, consistent with Markush practice outlined in MPEP 803.02.

Claims 6-13 and 17-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first and second paragraphs of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter

Art Unit: 1624

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Claims 14-16 specify certain CRF (corticotropin releasing factor) binding IC_{50} values. No compound according to the invention is described as having the property of being a ligand to the hormone corticotropin releasing factor itself. The compounds according to the invention are CRF *receptor* antagonists, that is, they bind to the CRF *receptor*, not to the hormone *per se*.

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for Formula I compounds, stereoisomeric forms, mixtures of stereoisomeric forms, and pharmaceutically acceptable salt forms thereof, does not reasonably provide enablement for prodrugs of Formula I compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Wands factors provide a guide for determining the scope of enablement provided by a given disclosure:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Art Unit: 1624

In re Wands, 858 F.2d 731,737 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

(A) Though it might appear that the scope of instant claims 1-4 is limited to chemical entities of Formula I, having the structure depicted, they are not. A prodrug, as defined by Bundgaard in:

Hans Bundgaard, Design of Prodrugs, page 1. © 1985 Elsevier Science Publishers.

“is an inactive species, and therefore, once its job is completed, intact prodrug represents unavailable drug.” Thus, an important requirement of prodrugs of chemical entities having the formula (1) is that they be pharmacologically inactive. Prodrugs come in myriad forms, and are not limited to only acylated derivatives, which are commonly cited as examples, and suggested as the preferred type of prodrug on page 15 of the instant specification. A prodrug may be an amide, a Mannich base (imine), an acyclic precursor to a cyclic compound, a polymer-bound drug (either covalently or ionically), a compound of the drug covalently or ionically bound to another drug with different action or a carboxylic acid which is decarboxylated to provide the active drug.

So, the scope of all prodrugs is quite broad. A prodrug does not necessarily even depend on the identity of the pharmacologically active agent formed from the prodrug for patentability. A prodrug, in other words, is not necessarily structurally related to the compound of which it is a prodrug, since the metabolism *in vivo* of that compound is what provides the drug.

(B) Prodrugs of a chemical entity having the Formula I are the nature of the invention.

Art Unit: 1624

(C) The state of the prior art with respect to the development of prodrugs is represented by:

Richard B. Silverman, The Organic Chemistry of Drug Design and Drug Action, pages 352-400. © 1992

Academic Press, Inc.

Silverman teaches many kinds of prodrugs, including all of the types mentioned above in section "(A)." Pages 353 and 354 list eight various reasons why a prodrug would be desirable. On page 354, Silverman teaches that some prodrugs are discovered accidentally, and some designed on the basis of known metabolic transformations.

(D) The level of ordinary skill in the art is that of a medicinal chemist, holding a graduate level degree in the field and with experience in preparative organic chemistry.

(E) As discovery of prodrugs is sometimes accidental, then it follows that whether a given compound will function as a prodrug or not is sometimes unpredictable. On the other hand, when a compound is designed as a prodrug, one must first understand the metabolic milieu into which the presumptive prodrug is to be introduced, and must also know to what extent the compound will be metabolized. The metabolism of xenobiotics is not always predictable. A prodrug must also, by definition, be pharmacologically inactive, so one must know which modifications of the structure of the parent compound will render it inactive. Structure-activity relationships must in large part be determined empirically, although once a rule is discerned, the structure-activity of a given series of compounds becomes predictable.

Theoretically, if one of ordinary skill in the art knew all of the above variables, prodrug structure could be predicted in advance. The reality is that all of these

Art Unit: 1624

considerations, in total, must be empirically derived when the compound in question is an allegedly novel compound, as are chemical entities of formula (1).

(F) Pages 22 and 23 of the instant specification include a brief description of what the inventor believes is necessary for one of ordinary skill to know in order to manufacture the claimed prodrugs. Only general statements along the lines of –

The term "prodrug" means compounds that are rapidly transformed in *viva* to yield the parent compound of formula I, for example by hydrolysis in blood. Functional groups which may be rapidly transformed, by metabolic cleavage, in *viva* form a class of groups reactive with the carboxyl group of the compounds of this invention. They include, but are not limited to such groups as alkanoyl (such as acetyl, propionyl, butyryl, and the like), unsubstituted and substituted aroyl (such as benzoyl and substituted benzoyl), alkoxycarbonyl (such as ethoxycarbonyl), trialkylsilyl (such as trimethyl- and triethylsilyl), monoesters formed with dicarboxylic acids (such as succinyl), and the like.

are provided as guidance.

No metabolic studies of the compounds *in vivo* have been done and no structure-activity rules are outlined – certainly no teaching as to which modifications will afford an *inactive* compound is found in the specification. The specification does not specifically address any type of prodrug other than acylated derivatives.

(G) No working examples, out of the six preparative examples, of a prodrug are in the disclosure.

(H) In order for one of ordinary skill in the art to practice the full scope of the prodrugs of chemical entities having the Formula I, a complete structure activity analysis of all of the entities falling within Formula I would have to be completed. This analysis

Art Unit: 1624

would involve thousands of individual compounds. The practitioner would first screen for which type of modifications of the molecular structure would render an inactive compound. Then, the metabolic studies of all of the inactive compounds would have to be completed, and compounds that are converted to active chemical entities of Formula I *in vivo* identified. This research would potentially be inconclusive and could take years. Additionally, one of ordinary skill in the art would necessarily have to undertake an effort to make totally new compounds not bearing any structural similarity to the chemical entities having the Formula I, such as the procyclic compounds converted to heterocyclic compounds *in vivo*, which are mentioned on page 360 of Silverman. Work with polymeric forms of the chemical entities having Formula I would be necessary also. Because different animals' metabolisms differ to the extent that xenobiotics are handled by different enzymatic pathways, this effort would have to be duplicated in each species for which a prodrug were sought. As evidence that animals will differ substantially in the manner that xenobiotics are metabolized, the examiner presents:

Al-Dabbagh and Smith, "Species differences in oxidative drug metabolism: some basic considerations."

Archives of toxicology. Supplement. Archiv fur Toxikologie. supplement, vol. 7, pages 219-231 (1984).

Al-Dabbagh and Smith states that the metabolic process itself is highly variable both between and within animal species, and that the toxic effect of many chemicals is a function of how the chemical is metabolized rather than the substance itself.

Given the amount of direction in the disclosure, this amount of experimentation is clearly undue. Applicants have not described the manner and process of making prodrugs of chemical entities having the Formula I, in such full, clear, concise, and exact terms as to enable any person skilled in the art to do so.

Art Unit: 1624

Claims 1-4 and 14-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claim 1 recites the term “prodrug.” As such, claim 1 and claims 2-4 and 14-16, dependent therefrom, are not of a clear and well-defined scope. The claims are drawn to chemical compounds which chemical compounds are prodrugs of the specified molecular structures. Although some fairly obvious “prodrug” candidates could be identified by one of ordinary skill (*e.g.*, esters), the *full scope* of *all* molecular structures which would yield a compound according to the instant claims upon metabolism in some (unidentified) animal is not readily apparent from a reading of the claims in light of the specification.

Simply because one of ordinary skill in the art understands what *function* a prodrug serves is not enough to apprise him of what molecular structures lie within the scope of claims 1-4 and 14-16 and what structures lie without the scope. The specification does not provide any teachings specifically applicable to the allegedly novel compounds disclosed therein which will render the claimed prodrugs.

A rejection of the term “prodrugs” under the first paragraph of this statute precedes this indefiniteness rejection of the same term. Applicants’ attention is directed to section “A” – the breadth of the claims – for an explanation of what is actually contemplated by “prodrug.” It is more than simply esters or amides of the compounds which have the specified molecular structures in the instant claims. This rejection is not being made in view of the breadth of the term “prodrug” but rather because of the

Art Unit: 1624

complexity that the term adds to the claim. One of ordinary skill in the art, to know what is actually being claimed, would have to be aware of all chemical compounds which can be metabolized into a compound having the specified molecular structures in any species. This is practically impossible.

Claim 1 (and claims dependent therefrom) are further indefinite because the definition of "modified monocyclic group" is not a proper Markush definition. The phrase "is selected from the group consisting of" is not recited in the first part of the group and the word "and" or "or" is not recited before the last member of the Markush group. The substitution with Y or $(CR_bR_b)_nZ$, therefore, only applies to the latter member of the group recited (heteroaryl).

Claims 14-16 are found to be further indefinite, in addition to being indefinite for depending from an indefinite base claim, because the conditions of the CRF binding assay by which the binding coefficients specified in those claims were determined are not provided in the claim. Differing assay conditions, such as pH, type of buffer, type of CRF (*i.e.* what species the hormone comes from), and temperature, will affect the IC_{50} value observed. Thus, claims 14-16 are indefinite.

Because it would be overly speculative for the examiner to do so, claims 14-16 have not been further examined on the merits. Upon amendment to overcome the indefiniteness and written description rejection of claims 14-16, those claims will be examined fully.

Art Unit: 1624

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

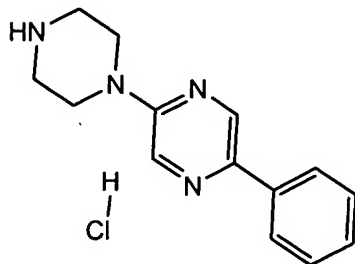
A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1 and 2 rejected under 35 U.S.C. 102(b) as being anticipated by US 4,081,542 (Lumma and Saari) or Lumma et al, "Piperazinylpyrazines with Central Serotoninmimetic Activity" Journal of Medicinal Chemistry, vol. 21(6), pages 536-542 (1978).

Both references disclose the compound 5-phenyl-2-(1-piperazinyl)pyrazine hydrochloride, having this structure:



The Lumma et al article reports this compound at page 540, in "Method E," and the Lumma and Saari patent discloses this compound in Example 20, column 6, in the table.

Art Unit: 1624

5-Phenyl-2-(1-piperazinyl)pyrazine hydrochloride anticipates claims 1 and 2 wherein Ar is aryl, R₁ and R₂ are hydrogen, X is heterocycloalkyl..

Claims 1-3 are rejected under 35 U.S.C. 102(e) as being anticipated by United States Patent Application Publication 2003/0018035 (Yoon et al). The application upon which the Yoon et al publication is based was filed 16 February 2001, before the domestic priority date of the instant application. Yoon et al actually claims domestic (provisional application filings) priority dates before 16 February 2001, but for the purpose of this Office action, only the filing date of the nonprovisional application is relied upon.

At page 18 of Yoon et al, two compounds according to claims 1-4 are disclosed:

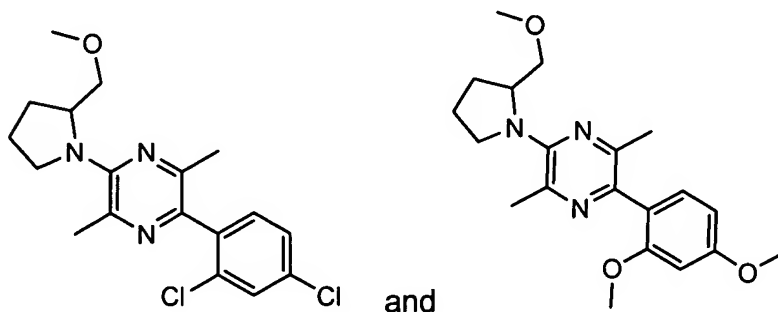
2-(2,4-dichlorophenyl)-5-[2-(methoxymethyl)pyrrolidin-1-yl]-3,6-dimethylpyrazine

and

2-(2,4-dimethoxyphenyl)-5-[2-(methoxymethyl)pyrrolidin-1-yl]-3,6-dimethylpyrazine

Both of these compounds are embraced by claims 1-4 wherein Ar is substituted aryl, R₁ and R₂ are methyl, X is pyrrolidine substituted with (CR_bR_b)_nZ – methoxymethyl.

The compounds have these respective structures:



Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over United States Patent Application Publication 2003/0018035 (Yoon et al).

Yoon et al is applied against claim 5 under 35 U.S.C. 103(a) as set forth above in the rejection of claims 1-3 under 35 U.S.C. 102(e).

At the time the invention was made, two compounds named in instant claim 5 would have been obvious to one of ordinary skill given the teaching of Yoon et al.

At Yoon et al's R₁ and R₃ positions in compounds of Formula Ia (page 6), Yoon et al's most preferred embodiment, which correspond to positions R₁ and R₂ of the instantly claimed compounds, which further correspond to positions numbered 3 and 6 in the named compounds according to instant claim 5, Yoon et al expressly suggests ethyl. The exemplified compounds of Yoon et al are substituted with methyl at the 3 and 6 position on the pyrazine ring, but ethyl is expressly suggested at page 6, section [0090] as a preferred group at those positions. Thus, for one of ordinary skill to make the corresponding 3,6-diethyl homologs of the two compounds pointed out in the rejection under 35 U.S.C. 102(e) above would clearly have been in the teaching of Yoon et al.

The motivation to do so would have been to make CRF receptor antagonist compounds, as taught by Yoon et al.

Abstract

The specification is objected to because the abstract of the disclosure does not convey a concise description of the invention. Reference only to "pyrazine derivatives" does not sufficiently describe to one of ordinary skill the nature of the invention disclosed. When the invention is a group of new chemical compounds, the generic structure of those compounds should be in the abstract. When the generic structure is in the abstract, searching the patent literature becomes more convenient for both the public and examiners at the U.S.P.T.O. See MPEP § 608.01(b).

Information Disclosure Statement

An Information Disclosure Statement filed 16 April 2004 is in the application file. All references in the application file and cited on the forms PTO-1449 accompanying the Information Disclosure Statement have been considered by the examiner. Items 20, 39 and 44 are improperly cited, as no pertinent passage in the reference has been pointed out (page numbers), so those items have not been considered by the examiner. Items 20-31, 41 and 44, in addition, are not in the file, so those references have not been considered either.

Allowable Subject Matter

Claim 4 would be allowable if rewritten to overcome the rejection under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Art Unit: 1624

The compounds named in claim 5, save for the first and third, are allowable over the cited prior art.

A pharmaceutical composition comprising allowable compounds is eligible for rejoinder with the examined claims, as well as a method of treatment comprising administering allowable compounds to a mammal. Methods of treating anxiety, depression and drug and alcohol withdrawal symptoms with a CRF receptor antagonist are deemed enabled by the disclosure. The full scope of the methods according to 7-9 is not enabled by the disclosure.

Methods of screening for CRF receptor ligands are not subject to rejoinder upon allowance of the claims of Group I.

Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Tuesday-Thursday from 8:00am to 4:30pm or Monday from 6:00am to 1:30pm. If Attempts to reach the examiner are unsuccessful, contact the examiner's supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

zt
